REMARKS

Claims 1-11 were pending in the application. Claims 1-4 have been cancelled as being directed to non-elected species. Claims 5 and 9 have been amended by the amendments presented herein and claims 6-8 and 10-11 have been cancelled without prejudice. New claims 12-16 have been added. Accordingly, once the amendments presented herein have been entered, claims 5, 9, and 12-16 will remain pending. Support for the new claims and the amendments to the claims can be found in the specification and claims as originally filed. No new matter has been added.

Restriction Requirement

In the response to the restriction requirement, Applicants elected the combination of genes set forth as SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19 and 21. Applicants would like to add SEQ ID NO:23 to this set to make the set of genes currently under examination SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21 and 23. As no art was identified by the Examiner that is relevant to SEQ ID NOs: SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19 and 21, Applicants believe that it would cause no additional burden on the Examiner to add SEQ ID NO:23 to the examined group.

Objection under 37 CFR 1.75(c)

The Examiner has objected to claim 10 under 37 CFR 1.75(c). Claim 10 has been canceled, thereby rendering this rejection moot.

Rejection under 35 USC Section 112, First Paragraph

The Examiner has rejected claims 5-9 under 35 USC 112, first paragraph as lacking enablement. Applicants respectfully traverse this rejection.

The Examiner has cited a number of references which suggest that the PLsis inducibility of a compound is dependent on many factors such as animal species, cell or tissue types, age, *in vitro* or *in vivo*, dose and the like, and alleges that one of ordinary

skill in the art would be required to undertake undue experimentation to practice the claimed invention which does not limit such factors.

A high-throughput *in vitro* assay system for evaluating the PLsis inducibility of compounds is highly demanded in the early stages of drug discovery, when a large number of compounds are screened, even if some evaluation results obtained by the assay system may not reflect *in vivo* PLsis inducibility of the compounds tested. In addition, taking into consideration the discrepancy between *in vitro* and *in vivo*, the specification defines "PLsis induction potential" separately from *in vivo* phenomenon. Namely, the gist of the present invention rests in the provision of evaluation results almost the same as those obtained by morphological observation using a microscope, by means of analyzing expression of twelve PLsis marker genes in a mammalian cell contacted with a test compound, thereby enabling evaluation of drug toxicity of compounds more rapidly, conveniently and accurately as compared to conventional *in vivo* or *in vitro* assay systems.

As regards animal species, a skilled artisan can easily identify a mammal to which the compound is to be administered. As regards cell type, he or she can also easily select a cell from among the cells derived from tissues or organs in which PLsis appearIn terms of the dose of compound, he or she can determine an appropriate dose from the therapeutically effective range.

As regards Nioi et al., contrary to the Examiner's allegation, it is Applicants' postion that this reference supports the enablement of the present invention. The results obtained using a fluorescent-labeled phospholipid in Nioi et al. (Fig. 1B) can be considered equivalent to those obtained by morphological observation using a microscope in the present invention, and therefore, the correct results. This means that amiodarone, amitriptyline, fluoxetine, imipramine, ketoconazole, sertraline, tamoxifen, citalopram, doxepin and quinidine are PLsis positive, and loratadine, acetaminophen, erythromycin and sotalol are PLsis negative. On the other hand, when the PLsis induction potential is predicted based on the values in TABLE 4 ("Average") wherein the standard value is 1.5, amitriptyline, fluoxetine, imipramine, ketoconazole, sertraline,

citalopram and doxepin are predicted to be PLsis positive, and amiodarone, loratadine, tamoxifen, acetaminophen, erythromycin, quinidine and sotalol are predicted to be PLsis negative. Therefore, the PLsis induction potential of 11 out of 14 compounds (i.e., 78%) is correctly predicted.

Furthermore, the standard value is not necessarily fixed to 1.5 according to the present invention. If a skilled artisan wishes to strictly exclude a candidate of PLsis positive compound, he or she can set the standard value to, for example, 1.3, based on the comparison of Fig. 1B and TABLE 4. In this case, since amiodarone, tamoxifen and quinidine are also predicted to be PLsis positive, all of 14 compounds are correctly predicted.

The usefulness of the inventive prediction method depends on how much it can correctly predict the appearance of myelin structure in a cell contacted with a test compound based on the standard value determined using a learning set consisting of known PLsis positive compounds and known PLsis negative compounds. For example, in Nioi et al., the compounds listed in TABLE 4 are grouped into "test compound set (from amiodarone to sertraline)" and "learning compound set (from tamoxifen to sotalol)". Based on the comparison of Fig. 1B and TABLE 4, a skilled artisan can set the standard value to 1.2 as a value capable of correctly judging PLsis induction potential of the compounds in the learning compound set by not less than 70%. When the average variation rates of the compounds in the test compound set are compared to the standard value, all of 7 compounds are correctly predicted. Thus, Nioi et al. does not deny but support the enablement of the present invention.

Rejections Under 35 USC 112, Second Paragraph

The term "compound" has been amended in the preamble of claim 7 to "test compound" in order to clearly distinguish it from "known PLsis inducing or non-inducing compounds" in step (1). Accordingly, Applicants believe that this rejection is rendered moot.

Rejections Under 35 USC 102 and103

The Examiner has rejected a number of claims under 35 USC 102 and 103. Applicants respectfully traverse this rejection. The features of claim 7 have been incorporated into claim 5. Accordingly, Applicants believe that this rejection is rendered moot. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

Conclusion

In view of the above arguments and amendments, Applicants believe the pending application is in condition for allowance. If a phone call with the Applicant's attorney would help to expedite prosecution, the Examiner is urged to contact the undersigned.

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Respectfully submitted,

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